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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,273	02/01/2002	Avi J. Ashkenazi	P3130R1C2	5808

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EXAMINER
CHERNYSHEV, OLGA N

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 07/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,273	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Olga N. Chernyshev	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal matters

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.

Respond to amendment

2. Claims 40-44 are pending and under examination in the instant office action.

3. The Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

5. Applicant's arguments filed on June 17, 2005 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections - 35 USC § 101

6. Claims 40-44 stand rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility for those reasons of record in section 6 of Paper mailed on March 16, 2005 and also in previous office actions of record.

Applicant traverses the rejection by discussing legal standards of 35 U.S.C. 101, refers to Utility Examination Guidelines and appropriate case law related to utility requirement (pages 3-4 of the Response). Applicant's review of the issue of utility and case law that has been cited is

not disputed by the Examiner. The disagreement, however, remains as to what constitutes a specific and substantial credible "real world" utility.

The claimed antibodies are asserted to be "useful in generating therapeutics for the treatment of pericyte-associated tumors as well as inhibiting angiogenesis, and facilitating purification of PRO444 for stimulation of angiogenesis" (bottom at page 5 of the Response). The Examiner maintains the position that these asserted utilities are not supported by any factual evidence of record or sound scientific reasoning in the instant specification, as filed. The only information presented in the instant specification regarding PRO444 polypeptide is disclosed in the Example 60, which shows that PRO444 polypeptide of SEQ ID NO: 9 induced the expression of c-fos in pericyte cells (page 142). Because many factors and signals have capability of activation c-fos and because the role of c-fos transcription factor is not limited to cancer (see reasons of record and references to scientific publication presented in the previous office actions of record), there is no scientific support for conclusion that activation of c-fos in pericytes by PRO444 is specifically associated with carcinogenesis of pericytes. Thus, the instant PRO444 polypeptides and claimed antibodies that specifically bind to PRO444 cannot be used for treatment of pericyte-associated tumors. Further, the instant specification provides no evidence or reliance to scientific publications to support a nexus between activation of c-fos in pericytes and angiogenesis. The art teaches that process of angiogenesis or neovascularization is very complex and that the involvement of pericytes in angiogenesis is controversial and not fully understood (see references of record in the previous office actions and also Diaz-Florez et al., Histol. Histopath., 1994, Vol. 9, pp.807-843, pages 807, 812 and 817-818 specifically). There appears to be no indication provided by Applicant or known in the art that would directly

connect activation of c-fos in pericytes and angiogenesis. Therefore, Applicant's asserted utilities, particularly in view of a lack of knowledge as to the biological significance of the polypeptide of SEQ ID NO: 9 with respect to cancer or angiogenesis constitutes a utility that requires further research to identify or reasonably confirm a "real world" context of use, see *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966).

Applicant submits a summary of arguments and the disputes issues involved at pages 5-6 of the Response. Applicant's arguments are answered in order as presented on pages 5-6 and further within the text of the Response.

Applicant submits that "The Examiner argues that there is no evidence that *c-fos* induction is associated with cancer or angiogenesis" (bottom at page 5), refers to articles by Saez et al., Marconcini et al. and McColl et al. and states that "one skilled in the art would believe that it is more likely than not that PRO444, an inducer of *c-fos* activity in cells having a known role in angiogenesis, (*i.e,* pericytes), is useful as an angiogenic factor" (page 7). However, Applicant mischaracterizes the Examiner's position. It was never argued by the Examiner that *c-fos* induction is not associated with cancer or angiogenesis. As fully explained earlier, the art recognizes that *c-fos* proto-oncogene plays a role in cell differentiation and transformation and because these processes are strongly related to tumor pathology, the role of c-fos transcription factor in cancer has been closely investigated. Further, the Examiner presented several review articles, which clearly explain that activation of immediate-early genes, such as *c-fos*, is caused by a wide variety of stimuli. For example, Janknecht et al. teaches that *c-fos* could be activated by growth factors, serum and UV-light; Herrera et al. indicates *c-fos* induction in response to seizures (see both articles cited with Paper mailed on April 28, 2004); *c-fos* could be induced by

increased intracellular calcium (Coulon et al, Paper mailed on March 16, 2005). Therefore, one skilled in the art would immediately appreciate that not every stimulus that results in activation of *c-fos* relates to its role in cancer, such role not currently fully established in the art. Applicant's reasoning and reference to publications of Saez et al. and Marconcini et al. (page 6 of the Response) does not substantiate for the link between activation of *c-fos* by PRO444 in pericytes and cancer of pericytes. With respect to publication of McColl et al., 2004 (top at page 7), Applicant is reminded that the utility of the claimed invention must be established and fully disclosed at the time of filing and, therefore, cannot be supported by reference to a post-filing disclosure.

At pages 7-8 of the Response, Applicant refers to *In re Oetiker* and *In re Brana* and submits that the evidentiary standard for utility is "a preponderance of the evidence", or "more likely than not" standard". Applicant further criticizes the references presented by the Examiner in the previous office actions of record stating that "the fact that other regulators of *c-fos* exist has no bearing on Applicant's asserted utilities (*e.g.*, as a diagnostic or therapeutic target for pericyte associated tumors, or as an angiogeneic agent). Applicants have provided evidence that PRO444 stimulates *c-fos* in pericyte cells" (middle at page 9). Applicant's arguments have been fully considered but are not persuasive for the following reasons.

It appears that Applicant has taken the position that because PRO444 activates *c-fos* expression in pericytes (with no comparison to other cell types), and because *c-fos* plays a role in cell differentiation/ transformation, than PRO444 could be used for treatment of pericyte-associated tumors. Also, again, because PRO444 activated *c-fos* expression in pericytes, and because pericytes are the cells present in blood vessel wall, than PRO444 is associated with

angiogenesis in pericyte cells. The issue, however, remains that at the time of invention, no disclosure in the form of factual data or reliance to scientific reasoning of relevance of *c-fos* activation by PRO444 polypeptides in pericytes to diagnosis or treatment of cancer in pericytes or formation of blood vessels has not been presented. The fact that PRO444 polypeptides induced *c-fos* in pericytes does not provide for immediate use of PRO444 specific antibodies for treatment of cancer or for inhibition of blood vessel formation. There is little doubt that, after complete characterization of the biological role of PRO444 in *c-fos* activation, this polypeptide and antibodies that specifically bind to it may be found to have a specific role in cancer and angiogenesis, which would support their specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. While an antibody that binds a polypeptide that has a stated correlation to a specific disease condition or physiological function would be considered a "substantial utility" in the context of identifying potential candidates for preventive or therapeutic measures, in the instant case the claimed antibodies are suitable only for additional research. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court expressed the opinion that all chemical compounds are "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediate obvious or fully disclosed "real world" utility.

To employ an antibody of the instant invention in methods of treatment of cancer conditions or for inhibition of angiogenesis, as currently asserted, would clearly be using it as the object of further research, which has been determined by the courts to be a utility, which, alone, does not support patentability. Since the instant specification does not disclose a credible "real

world" use for the PRO444 protein, which establishes the utility of the antibodies to PRO444, in their currently available form, then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. § 101 as being useful.

Claim Rejections - 35 USC § 112

7. Claims 40-44 stand rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a clear asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

8. No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (571) 272-0870. The examiner can normally be reached on 8:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Olga N. Chernyshev, Ph.D.
Primary Examiner
Art Unit 1649

July 19, 2005